~~Description~~

Process for preparing 3-chloro-5-nitrotoluene

Field of arts of the invention

The invention relates to a process for preparing 3-chloro-5-nitrotoluene and a process for preparing 3-chloro-5-methylphenylisocyanate.

Prior arts

JP-A 8-231489 and J. Med. Chem. 43, 4726-4737 (2000) show a process for preparing an isocyanate reacting with a polysaccharide and having a high separation power.

JP-A 8-231489 discloses a production process using potassium chloride in hydrochloric acid. The reference production process needs ~~any improvement~~to be improved because a strong acid is used and a salt formed by neutralization of the product mixture has to be treated.

J. Med. Chem. discloses a reaction of 4-methyl-2-nitroaniline with N-chlorosuccinic imide. In the reference reaction, purification with column chromatography is necessary to separate the intended product from a side-produced succinic imide. It is not suitable ~~to a large-scaled~~for large-scale production.

Summary of the invention

The invention relates to a process for preparing 3-chloro-5-nitrotoluene in mild conditions, without any strong acid and any strong base, to obtain an isocyanate precursor , and then a process for preparing 3-chloro-5-methylphenylisocyanate, which is useful ~~to produce~~in producing an optical separation agent.

The invention provides, as means to solve the above shown problems, a process for preparing 3-chloro-5-

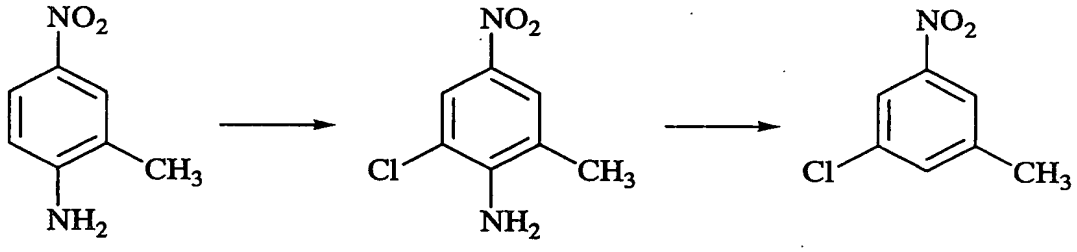
nitrotoluene, which comprises reacting 2-methyl-4-nitroaniline with a chlorinating agent in a neutral condition to obtain 2-chloro-4-nitro-6-methylaniline and deaminating the 2-chloro-4-nitro-6-methylaniline to obtain 3-chloro-5-nitrotoluene.

The invention provides, as means to solve another problem, a process for preparing 3-chloro-5-methylphenylisocyanate, which comprises reducing 3-chloro-5-nitrotoluene obtained by the above shown process and reacting the resulting product with triphosgene.

Detailed explanation of the invention

The preparation of 3-chloro-5-nitrotoluene will be explained in line with the following reaction formula 1.

Reaction formula 1




(1) (2) (3)

2-methyl-4-nitroaniline, (1) of the reaction formula 1, is first reacted with a chlorinating agent in a neutral condition to obtain 2-chloro-4-nitro-6-methylaniline, (2) of the reaction formula 1.

The reaction is preferably carried out in a solvent containing neither an acid nor a base at room temperature. The solvent is not particularly limited, as far as it is a solvent for both 2-methyl-4-nitroaniline and the chlorinating agent, ~~including~~and includes, for example, toluene, benzene, acetic acid, etc.

The chlorinating agent includes, for example, t-butylhypochlorite, N-chlorosuccinic imide, etc.

The reaction product of 2-chloro-4-nitro-6-methylaniline is isolated by filtering, etc., in advance to the subsequent reaction step. It may be washed or dried if necessary.

Then, 3-chloro-5-nitrotoluene, (3) of the reaction formula 1, is obtained from 2-chloro-4-nitro-6-methylaniline by deamination.

The deamination reaction for 2-chloro-4-nitro-6-methylaniline may proceed in a solvent such as ethanol or methanol. The reaction temperature is preferably controlled ~~into~~in plural steps in the following manner.

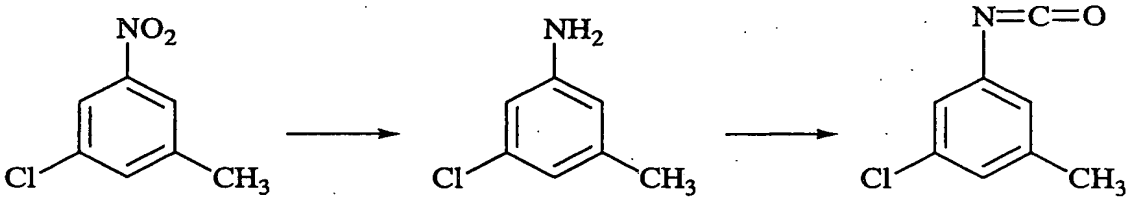
In the first step, the reaction mixture is adjusted between room temperature and 0°C, preferably 5 and 10°C, and then sodium nitrite is added thereto, preferably in the form of an aqueous solution of sodium nitrite of 1 to 2 mole equivalents.

In the second step, the reaction mixture is allowed to stand, preferably ~~stirred~~under stirring, at room temperature~~, it~~. It is observed that the temperature elevates up to about 45°C by way of the reaction heat and then decreases down to lower than 40°C, then the reaction mixture is stirred at a temperature of 40 to 50°C until no foaming occurs.

In the third step, the reaction mixture is cooled to room temperature and the reaction product is isolated by ~~filtering~~filtration or the like.

The preparation of 3-chloro-5-methylphenylisocyanate will be ~~below~~ explained below in line with the following reaction formula 2.

Reaction formula 2




(3) (4) (5)

3-chloro-5-nitrotoluene, (3) of the reaction formula 2, is first dissolved in a solvent such as ethanol and the solution is reacted, while being cooled, with a reducing agent (a hydrogenating agent) such as tin chloride or Raney nickel to obtain 3-chloro-5-methylaniline, (4) of reaction formula 2.

Triphosgene is dissolved in a solvent such as toluene and 3-chloro-5-methylaniline and a toluene solution of triethylamine are added thereto at room temperature ~~for reaction~~ to react and obtain 3-chloro-5-methylphenylisocyanate, (5) of reaction formula 2.

3-chloro-5-nitrotoluene, obtained by the preparation of the invention, is useful as a precursor to 3-chloro-5-methylphenylisocyanate. 3-chloro-5-methylphenylisocyanate is useful ~~to prepare~~in preparing conventional polysaccharides used as optical separating agents.

The process of the invention is carried out in mild conditions and suitable ~~to a large sealed~~for large scale production.

Example

The invention will be ~~below~~ explained below by reference to examples. The invention, however, is not limited by the examples.

Example 1 (preparation of 3-chloro-5-nitrotoluene)

① preparation of 2-chloro-4-nitro-6-methylaniline

2-methyl-4-nitroaniline (56.0g, 0.368mol) was dispersed in toluene (430ml) in a 1 liter four-neck flask. ~~Tirtiary~~Tertiary butyl hypochloride (46.0g, 0.423mol) was added dropwise thereto, while cooled in iced water and stirred. The mixture was stirred at room temperature for 3 hours. The ~~solid was~~solids were filtered and washed three times with 200 ml of a 50% aqueous ethanol three times. ~~It was~~They were then dried at 40°C at a reduced pressure to obtain 55.33 g of a yellow solid (production yield 80%). The yellow solid was used ~~at~~in the subsequent step without purification.

$^1$H-NMR, 500MHz, in $CDCl_3$ (δ)

8.12 (d, J = 2.2Hz, 1H)

7.92 (d, J = 2.2Hz, 1H)

4.73 (bs, 2H)

2.27 (s, 3H)

② preparation of 3-chloro-5-nitrotoluene

2-chloro-4-nitro-6-methylaniline (55.0g, 0.295mol) and ethanol (500ml) were mixed in a 2 ~~litter~~liter four-neck flask. A conc. Sulfuric acid (120ml) was added dropwise to the reaction mixture at a temperature ~~being~~ lower than room temperature. The reaction mixture was maintained at a temperature of 5 to 10°C and an aqueous solution of sodium nitrite (26.44g, 0.381mol/40ml) was added dropwise thereto over a period of 40 minutes.

The reaction mixture was then stirred at room temperature. It was observed that the temperature elevated up to 45°C by way of the reaction heat and then ~~decreases~~decreased down to lower than 40°C and then the reaction mixture was stirred at a temperature of 40 to 45°C until no foaming occurred.

The product mixture was cooled to room temperature and poured into 2500 ml of iced water to obtain precipitates. They were filtered and dried at a reduced pressure to obtain 45.95 g of a yellow solid (production yield 90%).

$^1$H-NMR, 500MHz, in $CDCl_3$ ($\delta$)

8.03 (bs, 1H)

7.94 (bs, 1H)

7.50 (bs, 1H)

2.46 (s, 3H)

Example 2 (preparation of 3-chloro-5-methylphenylisocyanate)

① preparation of 3-chloro-5-methylaniline

3-chloro-5-nitrotoluene (45g, 0.241mol) and ethanol (500ml) were mixed in a 2 ~~litter~~liter four-neck flask. The mixture was cooled to about 4°C. A solution of tin chloride monohydrate (217.67g, 0.965mol) in 200ml of ethanol was added dropwise to the mixture over 2 hours, while the reaction mixture was maintained at 10°C or lower.

Then the reaction product mixture was stirred at room temperature for 2 hours and poured into 2500 ml of iced water. It was neutralized with sodium hydroxide and filtered with a ~~nutsche~~nutsch filled with sellaite. The residue was washed with ethyl acetate. The intended product was obtained with ethyl acetate from the filtrate liquid.

Then the extract liquid and the washing liquid were ~~jointed~~joined. The mixture was washed with water and then ~~a~~ saturated salt water and dried with magnesium sulfate. ~~Concentrated~~After being concentrated, it was treated by distillation at a reduced pressure to obtain 28.0 g of a yellow liquid (production yield 80%).

B.p.:85-92°C/0.4kPa or lower (3Torr or lower)

$^1$H-NMR, 500MHz, in $CDCl_3$ (δ)

6.56 (bs, 1H)

6.48 (dd, JI, J2=1.3Hz, 1H)

6.36 (bs, 1H)

3.64 (bs, 2H)

2.22 (s, 3H)

② preparation of 3-chloro-5-methylphenylisocyanate

Triphosgene (17.01g, 0.0573mol) was dissolved in 200ml of ~~toluen~~toluene in a 1 liter flask. 150 ml of a toluene solution of 3-chloro-5-methylaniline (21.9g, 0.155mol) and triethylamine (36.0ml) was added dropwise thereto over 30 minutes at room temperature.

The reaction mixture was then stirred at 70°C for 2 hours and cooled to room temperature. The obtained precipitates of hydrochloric acid salt of triethylamine were filtered out and the filtrate liquid was concentrated and treated with distillation at a reduced pressure to obtain 16.87 g of a colorless liquid (production yield 65%).

B.p.: 72-74°C/0.53-0.66kPa (4-5Torr)

$^1$H-NMR, 500MHz, in $CDCl_3$ (δ)

7.00 (bs, 1H)

6.90 (bs, 1H)

6.80 (bs, 1H)

2.31 (s, 3H)